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<p>(54) Title: MR METHODS FOR IMAGING PULMONARY AND CARDIAC VASCULATURE AND EVALUATING BLOOD FLOW USING DISSOLVED POLARIZED <sup>129</sup>Xe</p>		
<p>(57) Abstract</p> <p>MR spectroscopy and imaging methods for imaging pulmonary and cardiac vasculature and the cardiac region and evaluating blood flow or circulatory deficits use dissolved phase polarized <sup>129</sup>Xe gas and large flip angle excitation pulses. Pulmonary and cardiac vasculature MRI images are obtained by delivering gas to a patient via inhalation such as with a breath-hold delivery-procedure, exciting the dissolved phase gas with a large flip angle pulse, and generating a corresponding image. Preferably, the image is obtained using multi-echo imaging techniques. Blood flow is quantified using low field MR spectroscopy and an RF excitation pulse with a frequency which corresponds to the resonance of the dissolved phase <sup>129</sup>Xe.</p> <div data-bbox="646 1178 1185 1787"> </div>		

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MR METHODS FOR IMAGING PULMONARY AND CARDIAC VASCULATURE AND EVALUATING BLOOD FLOW USING DISSOLVED POLARIZED  $^{129}\text{Xe}$ 

This invention was made with Government support under U.S. Air Force Grant number F41624-97-C-9001. The United States Government has certain rights in this invention.

5 Field of the Invention

The present invention relates to magnetic resonance imaging (“MRI”) and MR spectroscopy using hyperpolarized noble gases. More particularly, the present invention relates to imaging techniques using dissolved phase noble gases.

10 Background of the Invention

Conventionally, MRI has been used to produce images by exciting the nuclei of hydrogen molecules (present in water protons) in the human body. However, it has recently been discovered that polarized noble gases can produce improved images of certain areas and regions of the body which have heretofore produced less than satisfactory images in this modality. Polarized Helium 3 ( $^3\text{He}$ ) and Xenon-129 ( $^{129}\text{Xe}$ ) have been found to be particularly suited for this purpose. See U.S. Patent No. 5,545,396 to Albert et al., entitled "*Magnetic Resonance Imaging Using Hyperpolarized Noble Gases*", the disclosure of which is hereby incorporated by reference herein as if recited in full herein.

In order to obtain sufficient quantities of the polarized gases necessary for imaging, hyperpolarizers are used to produce and accumulate polarized noble gases. Hyperpolarizers artificially enhance the polarization of certain noble gas nuclei (such as  $^{129}\text{Xe}$  or  $^3\text{He}$ ) over the natural or equilibrium levels, *i.e.*, the Boltzmann polarization. Such an increase is desirable because it enhances and increases the

Magnetic Resonance Imaging ("MRI") signal intensity, thereby potentially allowing physicians to obtain better images of many tissues and organs in the body.

Generally stated, in order to produce the hyperpolarized gas, the hyperpolarizer is configured such that the noble gas is blended with optically pumped alkali metal vapors such as rubidium ("Rb"). These optically pumped metal vapors collide with the nuclei of the noble gas and hyperpolarize the noble gas through a phenomenon known as "spin-exchange". The "optical pumping" of the alkali metal vapor is produced by irradiating the alkali-metal vapor with circularly polarized light at the wavelength of the first principal resonance for the alkali metal (*e.g.*, 795 nm for Rb). Generally described, the ground state atoms become excited, then subsequently decay back to the ground state. Under a modest magnetic field (10 Gauss), the cycling of atoms between the ground and excited states can yield nearly 100% polarization of the atoms in a few microseconds. This polarization is generally carried by the lone valence electron characteristics of the alkali metal. In the presence of non-zero nuclear spin noble gases, the alkali-metal vapor atoms can collide with the noble gas atoms in a manner in which the polarization of the valence electrons is transferred to the noble-gas nuclei through a mutual spin flip "spin-exchange".

Conventionally, lasers have been used to optically pump the alkali metals. Various lasers emit light signals over various wavelength bands. In order to improve the optical pumping process for certain types of lasers (particularly those with broader bandwidth emissions), the absorption or resonance line width of the alkali metal can be broadened to more closely correspond with the particular laser emission bandwidth of the selected laser. This broadening can be achieved by pressure broadening, *i.e.*, by using a buffer gas in the optical pumping chamber. Collisions of the alkali metal vapor with a buffer gas can lead to a broadening of the alkali's absorption bandwidth.

For example, it is known that the amount of polarized  $^{129}\text{Xe}$  which can be produced per unit time is directly proportional to the light power absorbed by the Rb vapor. Thus, polarizing  $^{129}\text{Xe}$  in large quantities generally takes a large amount of laser power. When using a diode laser array, the natural Rb absorption line bandwidth is typically many times narrower than the laser emission bandwidth. The Rb absorption range can be increased by using a buffer gas. Of course, the selection of a buffer gas can also undesirably impact the Rb-noble gas spin-exchange by potentially introducing an angular momentum loss of the alkali metal to the buffer gas

rather than to the noble gas as desired. In any event, after the spin-exchange has been completed, the hyperpolarized gas is separated from the alkali metal prior to introduction into a patient.

Conventionally, gas-phase imaging has been possible using both  $^3\text{He}$  and  $^{129}\text{Xe}$ , and has been particularly useful in producing ventilation-driven images of the lungs, a region where proton images have produced signal voids. However, in contrast to gas phase imaging, dissolved phase imaging has proven to be problematic. Dissolved phase imaging uses the solubility characteristic of  $^{129}\text{Xe}$  in blood and lipid rich tissue. The gas phase is thus absorbed or "dissolved" into surrounding tissue or blood vessels and may allow perfusion imaging of the brain, lung, or other regions. Such images can potentially allow for the performance of non-invasive studies of the pulmonary vasculature to detect emboli and other circulatory system problems. Unfortunately, once the polarized gas has been dissolved (such as into the blood vessels), it has proven difficult to generate clinically useful images using the dissolved phase gas. Conventionally, dissolved phase imaging is attempted by performing a gas-based "regular" image and then looking for a spatially shifted dissolved phase image. However, the small flip angles typically associated with the "regular" image excitation pulses generally fail to produce sufficient detectable signal spectra in the dissolved phase, thus generating relatively inadequate dissolved phase images.

For example, MRI images using gas-space-imaging techniques have been generated using hyperpolarized  $^{129}\text{Xe}$  gas. See Mugler III et al., *MR Imaging and Spectroscopy Using Hyperpolarized  $^{129}\text{Xe}$  gas: Preliminary Human Results*, 37 Magnetic Resonance in Medicine, pp. 809-815 (1997). While good correlation is seen between the gas-space signal in the xenon images and the gas-space signal void in the proton images, the spectra associated with the dissolved phase signal components were significantly lower than the gas-phase signal.

In addition, conventional imaging with MRI units generally requires relatively large magnetic fields. For example, 1.5 Tesla ("T") units are common. The large magnetic fields can require special housing and shielding within the use site. Further, the MRI units must typically shim or control the magnetic field in order to produce magnet homogeneity which is suitable for imaging. As noted above, high field strength magnets generally require special handling and have relatively high operating

costs. Unfortunately and disadvantageously, both the high field strength magnet and the relatively high homogeneity requirements can increase the unit's cost both to the medical facility and ultimately, the consumer.

## 5 Objects and Summary of the Invention

In view of the foregoing, it is an object of the present invention to detect and/or manipulate dissolved-phase  $^{129}\text{Xe}$  signals in a manner that yields clinically useful images.

It is another object of the present invention to provide an imaging method  
10 which can obtain useful images of dissolved  $^{129}\text{Xe}$  in the pulmonary and/or cardiac  
vasculature.

It is an additional object of the present invention to provide an imaging method which yields useful images of the heart and major cardiac vessels using dissolved polarized  $^{129}\text{Xe}$ .

15 It is yet another object of the present invention to provide an imaging method which can obtain useful information and/or images of dissolved  $^{129}\text{Xe}$  which does not require high magnetic field strength and/or high magnetic field homogeneity.

It is a further object of the present invention to be able to obtain real-time blood flow path information such as local perfusion variation or blood flow abnormality using MR spectroscopy.

It is yet a further object of the present invention to provide an imaging method which can be used to determine quantitative measures of perfusion using dissolved polarized  $^{129}\text{Xe}$ .

These and other objects are satisfied by the present invention, which uses large flip angle (such as 90°) RF excitation pulses to excite dissolved phase gas in the pulmonary vasculature and MR data image acquisition techniques. In particular, a first aspect of the invention is directed to a method for obtaining MRI images using dissolved polarized  $^{129}\text{Xe}$ . The method includes positioning a patient in an MRI apparatus having a magnetic field associated therewith. Polarized  $^{129}\text{Xe}$  gas is delivered to the pulmonary region of the patient's body. Preferably, the  $^{129}\text{Xe}$  is inhaled and, due to the relatively high solubility of  $^{129}\text{Xe}$ , in a relatively short period of time, the inhaled polarized  $^{129}\text{Xe}$  gas enters into the body in the lung air spaces and either exists in the lung space as a gas and/or a gas which dissolves into adjacent

vasculature, tissues, spaces, or organs. Thus, the solubility of polarized  $^{129}\text{Xe}$  in the body is such that it generates an associated hyperpolarized gas imaging phase and a hyperpolarized dissolved imaging phase. A predetermined region (*i.e.*, a region of interest) of the patient's body which has a portion of the dissolved phase polarized gas  
5 therein is excited with a large angle (*e.g.* 90 degree) excitation pulse. At least one MRI image associated with the dissolved phase polarized gas is acquired after the excitation pulse. In a preferred embodiment, a multi-echo pulse sequence is used to generate an MR image. Further preferably, the excitation step is repeated within a predetermined repetition time. It is also preferred that the exciting step is performed  
10 so that the large angle pulse selectively excites substantially only the dissolved phase of the  $^{129}\text{Xe}$ .

Another aspect of the present invention is a method for evaluating (*e.g.*, measuring, determining, quantifying, observing, monitoring, imaging and/or assessing) the blood flow of a patient. A patient or subject having a pulmonary and  
15 cardiac vasculature is positioned in a MR (magnetic resonance) spectroscopy system. Polarized gaseous  $^{129}\text{Xe}$  is delivered to the patient or subject. The pulmonary and cardiac vasculature has an associated blood flow path and a portion of the polarized gaseous  $^{129}\text{Xe}$  is dissolved into the pulmonary (and/or cardiac) vasculature blood flow path. The blood flow of the subject can be evaluated (to determine, *e.g.*, xenon  
20 enhanced perfusion deficits, blood flow rate, blood volume, or blood flow path blockage) based on the spectroscopic signal of the dissolved  $^{129}\text{Xe}$  in the pulmonary (and/or cardiac) vasculature (*i.e.*, a portion of the circulatory system's blood flow path between and including at least portions of the lungs and heart). Preferably the evaluating step includes a measuring step and blood flow path blockage can be  
25 detected by comparing the blood flow rates of healthy subjects with the subject's measured flow rate.

An additional aspect of the present invention is directed toward a cardiac imaging method. The method includes positioning a subject in an MRI system and delivering polarized  $^{129}\text{Xe}$  thereto. At least a portion of the polarized  $^{129}\text{Xe}$  is  
30 dissolved into the cardiac blood flow path of the subject. The dissolved polarized  $^{129}\text{Xe}$  is excited with a large angle RF excitation pulse and a MR image associated with the excited dissolved polarized  $^{129}\text{Xe}$  is generated. Preferably, the excitation pulse is selectively delivered to a target area along the cardiac blood flow path and is

spatially limited to limit the depolarizing affect on the polarized gaseous  $^{129}\text{Xe}$  outside the target region.

Advantageously, unlike imaging the gas-phase  $^{129}\text{Xe}$  in the lung where conventionally small flip angles are used to avoid destroying the available  $^{129}\text{Xe}$  magnetization, there is minimal or no penalty for using a large flip angle excitation of the dissolved phase  $^{129}\text{Xe}$  because it will otherwise flow out of the chest region un-  
imaged. Indeed, a rapid large angle (such as 90 degree) pulse imaging sequence makes optimal use of the dissolved magnetization. The excitation repetition rate should be fast enough to capture the  $^{129}\text{Xe}$  before it flows out of the chest region.  
Such an imaging method can provide useful two (2) and three (3) dimensional dissolved phase images of the pulmonary and cardiac vasculature, images of anatomical features along the cardiac blood flow path, and patient blood flow rates and potential defects in the structure along the blood flow path of interest.

Further advantageously, blood flow abnormalities, perfusion variations (deficits or increases) and blood flow rate evaluation methods in spectroscopic systems according to the instant invention can be used in MRI units with reduced magnetic fields (such as 0.15 Tesla) and less restrictive homogeneity requirements. Further, the instant invention can use spectroscopic or MRI imaging techniques to obtain signal data corresponding to a quantity of dissolved polarized  $^{129}\text{Xe}$  before and after a physiologically active substance is administered to a human or animal body to evaluate the efficacy of the drug treatment or to quantitatively analyze a subject's blood flow.

The foregoing and other objects and aspects of the present invention are explained in detail herein.

#### Brief Description of the Drawings

**Figure 1** is a graph of 25  $^{129}\text{Xe}$  spectra (one spectrum per second) from the chest of a healthy human volunteer, showing the temporal evolution of the gas-phase and dissolved phase signal components during and after a 16-second breath-hold period.

**Figure 2** is a schematic diagram of the human body illustrating dissolution phase imaging according to the method of the present invention.



**Figure 3** is a graphical representation of a large angle radio frequency ("RF") excitation pulse sequence and exemplary corresponding echo sequences according to one of the methods of the present invention.

**Figure 4** is a schematic diagram of the human blood vascular system showing the dissolved  $^{129}\text{Xe}$  blood flow path according to one embodiment of a method according to the present invention.

**Figure 5** is a schematic diagram of the aorta shown of **Figure 4**.

**Figure 6** is a flow chart illustrating one embodiment of a method for spectroscopic imaging according to the present invention.

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#### Detailed Description of the Preferred Embodiments

The present invention will now be described more fully hereinafter with reference to the accompanying figures, in which preferred embodiments of the invention are shown. This invention may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein. Like numbers refer to like elements throughout. Layers and regions may be exaggerated for clarity.

As known to those of skill in the art, polarized gases are collected, frozen, thawed, and used in MRI applications. For ease of description, the term "frozen polarized gas" means that the polarized gas has been frozen into a solid state. The term "liquid polarized gas" means that the polarized gas has been or is being liquefied into a liquid state. Thus, although each term includes the word "gas", this word is used to name and descriptively track the gas which is produced via a hyperpolarizer to obtain a polarized "gas" product. Thus, as used herein, the term "gas" has been used in certain places to descriptively indicate a hyperpolarized noble gas product and may be used with modifiers such as solid, frozen, dissolved, and liquid to describe the state or phase of that product. Also, for preferred embodiments, the hyperpolarized gas is processed such that it is non-toxic and suitable for delivery to a human subject.

Various techniques have been employed to accumulate and capture polarized gases. For example, U.S. Patent No. 5,642,625 to Cates et al., describes a high volume hyperpolarizer for spin polarized noble gas and U.S. Patent No. 5,809,801 to Cates et al. describes a cryogenic accumulator for spin-polarized  $^{129}\text{Xe}$ . Co-pending U.S. Application Serial No. 08/989,604 to Driehuys et al., entitled "Methods of

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Collecting, Thawing, and Extending the Useful Life of Polarized Gases and Associated Apparatus”, describes an improved accumulator and collection and thaw methods. The disclosures of these documents are hereby incorporated by reference as if recited in full herein.

5           As used herein, the terms “hyperpolarize”, “polarize”, and the like, mean to artificially enhance the polarization of certain noble gas nuclei over the natural or equilibrium levels. Such an increase is desirable because it allows stronger imaging signals corresponding to better MRI (and spectroscopy) images of the substance and a targeted area of the body. As is known by those of skill in the art, hyperpolarization  
10 can be induced by spin-exchange with an optically pumped alkali-metal vapor or alternatively by metastability exchange. See Albert et al., U.S. Patent No. 5,545,396.

Referring now to the drawings, **Figure 1** illustrates the temporal evolution of the gas-phase and dissolved-phase signal components during and after a 16 second patient breath holding period as shown in Mugler III. et al., *supra*. The data  
15 acquisition began immediately after gas inhalation. The dissolved-phase spectra are shown on the left side of the figure. The vertical scale for the dissolved-phase spectra has been enlarged by a factor of ten over that of the gas-phase spectra (on the right side of the figure). As shown, peaks at approximately 185, 196, and 216 parts per million (“p.p.m.”) can be seen in the dissolved-phase spectra. The dissolved phase is  
20 thus shifted about 200 p.p.m. of chemical shift along the readout direction between the gas phase of xenon. These spectra were collected using a 10 degree hard RF pulse (so as to equally excite the gas and the dissolved phase components).

#### Imaging the Pulmonary Vasculature

25           The method of the instant invention recognizes that **Figure 1** indicates that the dissolved phase xenon signal strength appears to track very closely with the gas-phase signal strength. Accordingly, the present invention further finds that the close tracking of the signal strengths indicates extremely rapid equilibrium of the  $^{129}\text{Xe}$  concentration in the pulmonary blood with the  $^{129}\text{Xe}$  concentration in the lung. In  
30 addition, the instant invention recognizes that there is minimal or no build-up of dissolved  $^{129}\text{Xe}$  concentration over time. Thus, the instant invention incorporates the rapid equilibration and lack of magnetization build-up to provide improved imaging methods to obtain clinically useful dissolved phase  $^{129}\text{Xe}$  images.

Generally stated, in a preferred embodiment, a patient is positioned in an MRI unit and exposed to a magnetic field. The MRI unit typically includes a superconducting magnet, gradient coils (with associated power supplies), a surface coil (transmit/receive RF coil), and a RF amplifier for generating RF pulses set at  
5 predetermined frequencies. For  $^{129}\text{Xe}$  imaging at 1.5T field strength, the MRI unit is set to operate in the gas-phase at about 17.6 MHz. Preferably, the dissolved phase excitation frequency is shifted below the gas phase excitation frequency. More preferably the dissolved phase excitation is shifted to be about 200 ppm lower than the gas phase excitation frequency (corresponding to the chemical shift). Thus, in a  
10 preferred embodiment, the dissolved phase  $^{129}\text{Xe}$  RF excitation frequency is about 3.52kHz lower than the associated gas-phase excitation frequency. In yet another preferred embodiment, the imaging method employs a 17.6MHz gas phase excitation pulse and an associated dissolved phase excitation pulse of preferably about 17.59648MHz. Of course, the magnet field strength and excitation frequency can  
15 vary as is well known to those of skill in the art.

In any event, the RF pulse(s) is transmitted to the patient to excite the nuclei of the polarized  $^{129}\text{Xe}$ . The surface coil is tuned to a selected frequency range and positioned adjacent the targeted imaging region to transmit the excitation pulses and to detect responses to the pulse sequence generated by the MRI unit. Preferred  
20 surface coils for standard chest imaging include a wrap-around coil with conductors positioned on both the front and back of the chest. Examples of acceptable coils known to those of skill in the art include a bird cage configuration, a Helmholtz pair, a surface coil, and a solenoid coil (for permanent magnets).

The patient inhales a (predetermined) quantity of polarized  $^{129}\text{Xe}$  gas into the  
25 pulmonary region (*i.e.*, lungs and trachea). Preferably, after inhalation, the patient holds his or her breath for a predetermined time such as 5-20 seconds. This can be described as a "breath-hold" delivery. Examples of suitable "single dose" quantities of polarized gases for breath-hold delivery include 0.5, 0.75, and 1.0 liters of gas. Preferably, the dose at inhalation contains gas with a polarization level above 5%, and  
30 more preferably a polarization level above about 20%.

As schematically shown in **Figure 2**, subsequent to inhalation, at least a portion of the polarized gas enters into a dissolved state such that it enters the pulmonary vasculature, including the boundary tissue, cells, membranes, and

pulmonary blood vessels such as capillaries, venules, veins, and the like. A substantial amount of the dissolved polarized  $^{129}\text{Xe}$  which enters the pulmonary vasculature then ultimately enters the blood stream with an associated perfusion rate and cycles to the heart via the left atrium, then to the left ventricle and out through the aorta. In the methods according to the instant invention, the dissolved-phase  $^{129}\text{Xe}$  directly enters the venous side of the pulmonary vasculature. However, it is believed that information regarding the arterial side of the vasculature can be obtained due to the symmetry between the venous and arterial passages. For example, it is believed that if there were an arterial blockage, the method of the present invention can generate an "apparent" venous-side defect which corresponds to an "actual" arterial defect.

In overview, according to this preferred method of the instant invention, shortly after inhalation of a suitable amount of hyperpolarized  $^{129}\text{Xe}$  gas (or gas mixture), the MRI unit delivers a large flip angle RF excitation pulse to a selected portion of the pulmonary vasculature. As used herein, large flip angle means an angle which is greater than about 30 degrees. Preferably, the excitation pulse is greater than about 45 degrees. More preferably, the excitation pulse is greater than about 75 degrees and most preferably about a 90 degree excitation pulse. A 30 degree flip angle will generally yield about 50% as much signal as a 90 degree flip (45 degrees typically giving about 70% as much signal).

It is also preferred that the RF excitation is selectively performed. That is, that "selective excitation" is generated such that it excites only certain frequencies, *i.e.*, that it excites substantially only the dissolved phase polarized gas. An exemplary delivery of a selective excitation pulse is via a "hard" pulse. As used herein, "hard" pulse includes pulses where the RF is turned on for a short pulse time (" $t_{\text{pulse}}$ ") and then shortly thereafter, indeed preferably substantially "instantly", turned off. However, short pulse times can yield uncertainty in the associated frequency it generates. Therefore, in a preferred embodiment, selective excitation is performed such that the pulse frequency is centered on the dissolved gas phase resonance desired (*i.e.*, 17.59648 MHz) and has a pulse time,  $t_{\text{pulse}}$ , such that the associated frequency is below the corresponding gas phase excitation frequency (*i.e.*, 17.6 MHz). For example, one frequency spectrum of a square excitation pulse having a time  $t_{\text{pulse}}$  and which is centered on a frequency (" $f_0$ ") can be described by the equation:

$\sin(a(f-f_0)/a(f-f_0))$ , where  $a = 3.1416 \cdot t_{\text{pulse}}$ .

Therefore, the pulse time  $t_{\text{pulse}}$  is preferably set so that the  $\sin(a(f-f_0))=0$  for the gas phase component. Stated differently, the pulse time  $t_{\text{pulse}}$  is determined according to the relationship  $t_{\text{pulse}} = 1/(f-f_0)$ . In one embodiment, for a 1.5T magnetic  
5 field strength,  $f-f_0$  equals 3.52kHz and  $t_{\text{pulse}}$  is about 284  $\mu$ seconds ( $10^{-6}$ ). Of course, as will be recognized by those of skill in the art, alternative approaches can also be used, such as but not limited to, sine pulses, gaussian pulses, and the like.

In a preferred embodiment, the selective excitation is timed such that it excites the entire pulmonary blood volume. The pulmonary blood volume includes the  
10 volume of blood which fills the blood passages associated with the circulatory system between and/or within the lungs and the heart (which can include the volume of blood or a portion of the volume of blood within the boundary lung tissue and/or heart). More preferably, in the method of the present invention, the blood volume of interest is estimated as about half the volume between the right ventricle and the left atrium  
15 (because of the expected  $T_1$  of the dissolved phase polarized  $^{129}\text{Xe}$  in the blood, it is likely that only the venous side of the circulatory system will include  $^{129}\text{Xe}$  with sufficient polarization levels to provide detectable signal strength). Exemplary volumes will be discussed further below. Advantageously, unlike imaging the gas-phase  $^{129}\text{Xe}$  in the lung where conventionally small flip angles are used to avoid  
20 destroying the available magnetization, there is minimal and most likely no penalty for using a large flip angle excitation of the dissolved phase  $^{129}\text{Xe}$  in the pulmonary vasculature because the magnetization will otherwise flow out of the chest region unimaged. Further, according to the preferred method of the present invention, "fresh" magnetization is substantially continuously flowing in from the capillary beds during  
25 the procedure.

The present invention is preferably employed to evaluate blood flow throughout the pulmonary and cardiac vasculature and/or to evaluate blood flow in particular localized regions of the pulmonary and cardiac vasculature. The term "pulmonary and cardiac vasculature" as used herein includes all of the blood vessels  
30 within the lungs and/or heart, the chambers of the heart, the passages between the chambers of the heart, as well as the blood vessels between the lungs and heart, and blood vessels between the lungs or heart and other tissues and/or organs. The pulmonary and cardiac vasculature includes, but is not limited to, the pulmonary veins

and arteries and associated capillaries, the left and right atria of the heart, the left and right ventricles of the heart, the myocardium, the aorta and aortic arch, the coronary artery, the coronary arteries, the subclavian arteries, and the carotid arteries.

More preferably, the imaging methods of the present invention are carried out to provide clinically useful images of the left and right pulmonary veins and associated capillaries, the left atrium and left ventricle, the myocardium, the ascending aorta, the coronary arteries, the aortic arch, the descending aorta, the left and right subclavian arteries, and the left and right carotid arteries.

Immediately upon inhalation of hyperpolarized  $^{129}\text{Xe}$  into the lungs, Xe begins to dissolve into the pulmonary blood stream. The concentration of Xe in the pulmonary capillary beds (" $[\text{Xe}]_p$ "), can be assumed to equilibrate instantaneously with the concentration of Xe in the lung gas spaces (" $[\text{Xe}]_L$ "), thus the relationship can be stated as:

$$[\text{Xe}]_p = \lambda [\text{Xe}]_L \quad (1)$$

where " $\lambda$ " is the Xe blood/gas partition coefficient or blood solubility. This concentration can be expected to equilibrate in the venous side of the pulmonary vasculature just a few seconds after inhalation as will be discussed further below. The standard unit for concentration is an "amagat" which refers to 1 atmosphere of gas pressure at a temperature of 273K. For humans whose lungs contain one atmosphere of gas and whose temperature is about 310K, all gas densities should be scaled down by a factor of about  $A=0.88$  amagat per atmosphere. For a patient inhaling a volume (" $V_{\text{Xe}}$ ") of Xe into their lungs of volume (" $V_L$ "), the resulting Xe density in the lung  $[\text{Xe}]_L$  will be

$$[\text{Xe}]_L = A \frac{V_{\text{Xe}}}{V_L} \quad (2)$$

Thus, the concentration of Xe in the pulmonary blood  $[\text{Xe}]_p$  will be related to the inhaled gas volume  $V_{\text{Xe}}$ , and can be stated by the expression:

$$[\text{Xe}]_p = \lambda A \frac{V_{\text{Xe}}}{V_L} \quad (3)$$

For reference, an estimate of  $\lambda$  for Xe in blood is that  $\lambda \approx 0.15$ . Thus, as an example, a patient who inhales 1L of Xe into his 6L lung will yield a Xe density in the lungs of  $[\text{Xe}]_L \approx 0.15$  amagat, and correspondingly a Xe density in the pulmonary capillary beds of  $[\text{Xe}]_P \approx 0.02$  amagat. Thus, the dissolved polarized  $^{129}\text{Xe}$  gas in the

5 pulmonary capillary beds is approximately 1/6 the concentration of the lung gas.

In operation, upon crossing the gas/blood barrier, the dissolved polarized  $^{129}\text{Xe}$  is transported out of the lung into the heart and then out to the remainder of the body. However, as noted above and generally stated, once the  $^{129}\text{Xe}$  has been transported out of the heart, it is likely that it will no longer be useful for pulmonary or cardiac

10 imaging. Therefore, it is preferred that the imaging is performed in a manner which uses the polarization before it is transported out of the heart and dispersed into the body, potentially resulting in a loss of the useful pulmonary (and/or cardiac) vasculature magnetization.

The timescale for  $^{129}\text{Xe}$  transport out of the pulmonary region or chest area

15 ("t<sub>p</sub>") is a function of pulmonary blood flow rate ("Q") and pulmonary blood volume ("V<sub>p</sub>") which can be expressed by the following:

$$t_p = \frac{V_p}{Q} \quad (4)$$

Thus, to determine t<sub>p</sub>, one can assume that the volume of pulmonary venous

20 blood between the lung and the heart ("V<sub>p</sub>") is such that V<sub>p</sub> ≈ 200 cubic centimeters ("cc") and that the pulmonary blood flow rate (Q) is approximately Q ≈ 80 cc/s. See R.M. Berne, *Physiology* (Mosby-Yearbook, Inc., St. Louis, Mo., 3d ed. 1993). With these numerical assumptions, the transit time from lung to heart is determined to be less than 3.0 seconds, and more particularly t<sub>p</sub> ≈ 2.5 seconds. Of course, as will be

25 understood by those of skill in the art, alternative blood volumes will yield alternative transit times. For example, another conventional source estimates a blood flow of about 5.5L/min (92cc/sec) and a total blood volume in the pulmonary vessels at any one time of about 1.0L (of which 100ml are in the capillaries). According to one

30 method of the instant invention, the relevant blood volume would be 500ccs from the lung to the heart and the time from dissolution to entry into the heart is then about 5

seconds. Correspondingly, the transit time out of the capillaries is then about 0.5 seconds. Thus, the image sequence will depend on the imaging region or volume of interest. Further, as will be appreciated by those of skill in the art, children and smaller adults can have less volume while larger adults can have more, and the corresponding image times can vary accordingly.

In a preferred imaging method of the instant invention, the delay between the large angle (preferably 90 degree) RF excitation pulses is preferably less than  $t_p$ . As will be discussed below, it may be advantageous to further shorten this delay time. In any event, for  $T_R$  less than or equal to the time  $t_p$ , signal strength in the (perfusion) image will be substantially linearly proportional to the inhaled gas volume and the  $^{129}\text{Xe}$  polarization level of the inhaled gas.

Accordingly, care should be taken when setting the excitation pulse repetition interval  $T_R$ . This is because the setting of  $T_R$  will affect both image SNR and determine, to some extent, which parts of the lung or cardiac vasculature will be visualized. A long  $T_R$  will result in  $^{129}\text{Xe}$  polarization or magnetization that is (uniformly) distributed throughout the venous side of the pulmonary vasculature. A very short  $T_R$  setting results in imaging Xe substantially in the capillary beds of the lungs. This is because the large flip angle pulse substantially destroys the incoming  $^{129}\text{Xe}$  polarization or magnetization before it reaches the larger vessels and thus the larger blood vessels would not be rendered visible. Therefore, if it is desired to emphasize or detect emboli in the smaller capillaries, one can restrict imaging to the smaller vessels by using short repetition times, and even if the small vessels cannot be resolved individually, a perfusion-associated defect should nonetheless be detectable.

As shown in **Figure 3**, the excitation pulse repetition time ( $T_R$ ) is associated with either a single echo or multi-echo pulse acquisition sequence. For each RF pulse, a multi-echo data acquisition is preferably performed such that there are at least four received echoes between each excitation pulse. Preferably, for a breath-hold delivery of 10 seconds, four RF dissolved phase excitation pulses (about 2.5 seconds apart) are generated. Further preferably, for each RF pulse, at least 32 corresponding echoes are generated. Further, because increasing numbers of echoes will allow increased amounts of signal to be extracted from the dissolved gas. Thus, for example, for a 10 second breath-hold delivery and a  $T_R$  of 2.5 seconds, for 128 echoes



collected for each RF excitation, the SNR can be improved by a factor of 2 over the 32 echo pulse embodiment described above.

The repetition time  $T_R$  of **Figure 3** is preferably 0.01-3.0 seconds. In one embodiment, for single echoes, the repetition time between excitation pulses is set at  
 5 78ms or less as will be discussed further below. More preferably, the repetition time is set such that it corresponds to the time it takes for a given volume of blood to move from the lungs to the heart (" $t_p$ "), estimated as stated above at under 3.0 seconds and preferably at about 2.5 seconds. Further, the repetition time can be adjusted to image specific portions of the pulmonary region. For example, the repetition time can be  
 10 decreased to emphasize a signal from capillaries in the pulmonary region. In contrast, the repetition time can be increased to emphasize vasculature which is a further distance from the pulmonary region.

Unlike imaging the gas-phase of the polarized  $^{129}\text{Xe}$  in the lung, where conventionally small flip angles are used to avoid destroying the available  
 15 magnetization, there is minimal or no penalty for using a large flip angle excitation of the dissolved phase polarized  $^{129}\text{Xe}$  because it will otherwise flow out of the chest region un-imaged. Indeed, a rapid 90 degree pulse imaging sequence makes optimal use of the dissolved  $^{129}\text{Xe}$  polarization or magnetization. The excitation repetition rate should be fast enough to capture the  $^{129}\text{Xe}$  before it flows out of the chest region.  
 20 Such an imaging method can provide two (2) and three (3) dimensional dissolved phase images of the pulmonary vasculature.

In a preferred embodiment, an entire perfusion image (MR image directed to the dissolved phase polarized gas) is generated in a single breath-hold period (" $T_B$ "). For example, one can use a slice-selective image in which the chest is divided into a  
 25 number of slices (" $N_s$ "). A typical MR image slice comprises a number of phase encode steps (" $N_{pe}$ ") and a number of frequency encode steps (" $N_{fe}$ "). Typical numbers of these steps are  $N_{pe} = 128$  and  $N_{fe} = 128$  (or 256). For single echoes derived from each excitation, 128 separate RF excitations can be used to generate a single image. Single echoes may be preferred where there are relatively short  $T_2^*$   
 30 periods (dissolved phase transverse relaxation times) or adverse blood flow effects.

The number of RF pulses (" $N_{rf}$ ") which can be generated in a single breath-hold time is related to repetition time ( $T_R$ ) and breath-hold time ( $T_B$ ), and can be expressed by:

$$N_{rf} = \frac{T_R}{T_R} \quad (5)$$

Accordingly, for illustrative purposes, for single-echo imaging with a breath-hold period  $T_B = 10s$ , then the repetition time is preferably set such that  $T_R \leq 78ms$  for a single image slice.

In view of the foregoing, the signal strength expected in a given image voxel can be analyzed as a function of the image parameters. The effective pulmonary volume imaged (" $V_{eff}$ ") can be determined by blood flow rate ( $Q$ ) and pulse repetition time ( $T_R$ ), expressed by the following:

$$V_{eff} = T_R Q \quad (6)$$

To calculate the polarization or magnetization in a given pulmonary voxel (" $V_{ip}$ ") one can divide the effective pulmonary image volume ( $V_{eff}$ ) by the image matrix size, as expressed by equation (7).

$$V_{ip} = \frac{T_R Q}{N_s N_{pe} N_{fe}} \quad (7)$$

The total signal in each pulmonary vasculature voxel (" $S_{ip}$ ") is proportional to the product of coil gain (" $G$ "),  $^{129}\text{Xe}$  polarization (" $P_{Xe}$ "), the concentration or density of  $^{129}\text{Xe}$  in the vasculature ( $[Xe]_p$ ), voxel volume (" $V_{ip}$ "), and the sine of the excitation angle used in the pulmonary vasculature (" $\sin \alpha_p$ "). Thus, the relationship can be expressed as follows:

$$S_{ip} = \frac{GP_{Xe}\lambda[Xe]_p T_R Q \sin \alpha_p}{N_s N_{pe} N_{fe}} \quad (8)$$

Similarly, the signal strength per voxel of  $^{129}\text{Xe}$  in the lung (" $S_{il}$ ") can be stated by equation (9) (the expression " $\sin \alpha_L$ " representing the excitation angle used in the lung).

$$S_{il} = \frac{GP_{Xe}[Xe]_l V_l \sin \alpha_l}{N_s N_{pe} N_{fe}} \quad (9)$$

Comparing the signal strength in equations (8) and (9) gives a ratio of signal strengths  
 5 per voxel of dissolved versus gaseous polarized  $^{129}\text{Xe}$  as stated in equation (10).

$$\frac{S_{ip}}{S_{il}} = \frac{\lambda T_R Q \sin \alpha_p}{V_l \sin \alpha_l} \quad (10)$$

As an example, for 128 phase encoding steps, the gas phase image can be made with  
 $\alpha_l = 7^\circ$  and the perfusion image with  $\alpha_p = 90^\circ$ . Thus, in this example, for  $T_R = 78$  ms,  
 10 as calculated above for single-echo imaging, then the relative signal strengths can be  
 estimated as follows:

$$\frac{S_{ip}}{S_{il}} = \frac{.15 \times .078 \times 80 \text{ cm}^3 \text{ s}^{-1}}{6000 \text{ cm}^3 \times 0.12} \approx 1 \times 10^{-3} \quad (11)$$

While the signal strength per voxel is dramatically lower in the dissolved  
 phase than in the gas phase, this lower signal strength does not prevent clinically  
 15 useful perfusion imaging according to the instant invention as described herein.

Additionally, steps can be taken to increase the signal per voxel for the  
 perfusion imaging of the pulmonary vasculature as described above. First, one may  
 choose to decrease image resolution to increase signal strength. In one embodiment,  
 for example, one may choose not to perform slice-selective imaging. A full  
 20 projection image of the chest reduces the number of image slices (" $N_s$ ") to  $N_s = 1$   
 from  $N_s = 16$  for slice-selective imaging with 1 cm thick slices. Further, the  
 frequency-encode steps ( $N_{fe}$ ) combined with the non-slice selective imaging yields a  
 factor of 32 SNR increase per voxel in the perfusion image.

A reduction in the number of phase encode steps has two beneficial effects on  
 25 image SNR. First, a reduction by 2 of  $N_{pe}$  gives a factor of 2 increase in voxel SNR  
 akin to reducing  $N_{fe}$ . Furthermore, in the single-echo imaging discussed so far, a

reduction in  $N_{pe}$  implies a corresponding reduction in the number of RF excitations required  $N_{rf}$ . This allows us to increase the repetition time  $T_R$ , which allows more time for magnetization to flow from the lung into the pulmonary vasculature.

Accordingly, reducing  $N_{pe}$  by 2 provides another factor of 4 in SNR per voxel,

- 5 bringing the total signal gain per voxel to 128. Thus, with some resolution sacrifice, signal strengths per voxel of  $^{129}\text{Xe}$  in the pulmonary vasculature can be about 8%-10% or more of the corresponding voxel signal strength in the lung (*i.e.*,  $S_{ip} \approx 0.1 S_{il}$ ).

- The image matrix of Mugler III *et al.* was  $64 \times 128 \times 11$  for a gas phase image of the lung. The voxel SNR was 32 for this image. Given this data and the steps  
10 suggested above, a dissolved phase image of the pulmonary vasculature, using single-echo  $90^\circ$  excitations spaced 78ms apart can be made with a matrix size of  $64 \times 64 \times 1$  with an SNR of 1.6 in each voxel. Further, as described in co-pending application to Driehuys *et al.*, "Methods of Collecting, Thawing, and Extending the Useful Life of Polarized Gases and Associated Apparatus", (incorporated by  
15 reference hereinabove), reliable  $^{129}\text{Xe}$  polarizations of well above 10% are now achievable. This is in comparison to the 2% polarization level described in the Mugler III *et al.* disclosure. In addition, various surface coil improvements such as tuning, configuring the coil to have close physical alignment with the body volume of interest, new coil technology known to those of skill in the art as circular  
20 polarization ("CP"), and the like, can yield another factor of  $2\sqrt{2}$  improvement. Thus, and advantageously, this permits an increase in SNR (an improvement of about 30 is possible), indicating that a pulmonary image of the stated matrix size ( $64 \times 64 \times 1$ ) can be made with a voxel SNR of about 45.

- Signal to noise ratio ("SNR") improvements in the images can be obtained by  
25 using one or more of thick slices (no slice select), reduced image matrix size, multi-echo imaging, and signal averaging. In addition, when multiple echoes ( $N_e$ ) are used, the number of RF excitation pulses can be decreased. Further, alternative imaging strategies can be used. For example, for multiple echoes (1)  $T_R$  can be kept constant and more images can be generated (multi-slice, dynamic imaging, etc.) (2)  $T_R$  can be  
30 lengthened and thus more area of the vasculature can be imaged, and (3)  $T_R$  can be kept constant and the multiple echoes can be used to average lines in k-space to increase the image SNR. For example, if four echoes are made from each excitation,

the same line in k-space can be imaged four times on each excitation and thereby advantageously increase the image SNR by 2.

As noted above, further signal gains can be obtained if multi-echo imaging strategies are successfully implemented. Therefore, and preferably, the MRI unit  
5 generates subsequent multi-echo image acquisition. although a single echo imaging is also possible as described above. For  $^{129}\text{Xe}$  dissolved in blood, it is expected that the transverse relaxation time (" $T_2^*$ ") is relatively long (on the order of 100ms or more). In the absence of undesirable flow effects, one can generate multiple echoes within this time. Each echo generated is preferably a phase-encode step. As an estimate, one  
10 can make as many as 30 echoes in 100ms. This number of echoes can allow a large reduction in the number of RF excitations ( $N_{rf}$ ) and thus further lengthen the repetition time ( $T_R$ ), and increase the SNR per voxel. Preferably, the upper limit for the repetition time of  $T_R$  is to set it equal to the blood transit time out of the lung  $t_p$ . For  $T_R = t_p = 2.5$  s is set as discussed above, then four RF excitations can be generated  
15 during a 10 second breath-hold period. In order to generate 128 phase encode steps, 32 echoes per excitation are used. Therefore, for 32 echoes, the SNR per voxel is increased by a factor of 32 ( $2500/78 = 32$ ) over the single echo imaging technique described above. That is, the signal gain is linear with echo number, and preferred imaging methods of the instant invention include multi-echo imaging. With such a  
20 signal increase, the previous estimate suggests that the image matrix size can be increased to  $128 \times 256 \times 10$  with a voxel SNR of 8. Thus, multi-echo imaging can allow slice-selective imaging as well.

Preferably, when multi-slice imaging is employed, the slice acquisition is performed by interleaving the slices. A slice-selective acquisition will only excite  
25 spins in a given slice of the lung. Once a slice has been excited (and a line of k-space) has been obtained, that slice is not excited again until the time  $T_R$  has elapsed and spins (in the magnetized polarized dissolved gas) have flowed back into the slice. However, alternate slices can be excited and imaged during this "waiting" period. Advantageously, such interleaving of slices allows image acquisition time to be  
30 minimized.

One concern for multi-echo imaging methods is the flow of blood and the affect on the ability to (re)focus the echoes. Thus, multi-echo imaging methods may be facilitated by the use of cardiac-gated imaging, and to do all imaging during

diastole, the period when blood flow is slowest. In one embodiment, cardiac gating is used to better time/sequence image acquisition to correspond with the period of slow blood flow in the patient. Alternatively, other methods of slowing the blood circulation such as delivering sedatives or anesthesia to the patient to slow the heart rate may be employed to facilitate multi-echo image acquisition.

As will be appreciated by those of skill in the art, imaging with polarized dissolved gas depends on transport of sufficient surviving polarization or magnetization to tissues of interest. In a preferred embodiment, the tissues of interest include the pulmonary region, and particularly the pulmonary vasculature. As will also be appreciated by those of skill in the art, polarization decays corresponding to the longitudinal relaxation time, T<sub>1</sub>. Dissolved phase <sup>129</sup>Xe can have a relatively short relaxation time (T<sub>1</sub>) generally thought to be due to the presence of oxygen and due to paramagnetic deoxyhemoglobin in the blood. For example, T<sub>1</sub> for substantially fully oxygenated human cell membranes is estimated at about 15 seconds. Alternatively, T<sub>1</sub> in blood has also been estimated as about 5 seconds. See A. Bifone et al., 93 Proc. Natl. Acad. Sci., p. 12932 (1996). Taking the estimated upper limit of about a five second transit time to the heart as discussed above, the xenon polarization can be attenuated to about 1/3 of its starting value at the heart. This relationship supports that T<sub>R</sub> should be shortened to less than about 2.5 seconds, and preferably less than about 1-2 seconds. Correspondingly, with about a 2.5 second transit time, the magnetization can be calculated as noted above to be about 0.61 of its starting magnetization.

As is also known to those of skill in the art, the polarized <sup>129</sup>Xe also has an associated transverse relaxation time, T<sub>2</sub>. In the dissolved phase, as noted above, it is estimated that this T<sub>2</sub><sup>\*</sup> is relatively long. Taking advantage of this characteristic, it is preferred that (especially for T<sub>2</sub><sup>\*</sup>'s which are greater than about 100ms), multi-echo acquisition methods are used. As will be appreciated by those of skill in the art, examples of suitable multi-echo methods include Echo Planar Imaging ("EPI"), Rapid Acquisition with Relaxation Enhancement ("RARE"), FSE ("Fast Spin Echo"), Gradient Recalled Echoes ("GRE"), and BEST. Examples of some suitable pulse sequences can be found in an article by John P. Mugler, III, entitled *Gradient-Echo MR Imaging*, RSNA Categorical Course in Physics: The Basic Physics of MR Imaging, 1997; 71-88. For example, the article illustrates an example of a standard

single RF spin-echo pulse sequence with a 90 degree excitation pulse and a 180 degree refocusing pulse. In this diagram,  $G_P$  is a Phase-encoded gradient,  $G_R$  is the readout gradient,  $G_S$  is the section-select gradient, and RF is the radio frequency. The article also illustrates a Gradient Recalled Echo pulse sequence (GRE) with a flip angle  $\alpha$  and a Rapid Acquisition with Relaxation Enhancement (RARE) pulse sequence as well as a single shot Echo Planar Imaging (EPI) pulse sequence with gradient recalled echoes.

In summary, according to a preferred embodiment of the pulmonary vasculature imaging method of the present invention, a single breath inhalation volume "V<sub>xe</sub>" of about 0.5-1.25 liters of polarized  $^{129}\text{Xe}$  is delivered to a patient for a breath-hold time  $T_B$  of about 5-15 seconds. Longer breath-hold times will allow an increased dissolved-phase polarized gas perfusion signal to be extracted from the polarization or magnetization delivered via the lung. In this embodiment, the large flip angle excitation pulse (" $\alpha_P$ ") is about 90°. Preferably, the excitation pulse is tailored in frequency and duration to affect only the dissolved  $^{129}\text{Xe}$  ("selective excitation"), leaving the gas-phase magnetization in the lung substantially undisturbed.

Thus, during the breath-hold period, the hyperpolarized  $^{129}\text{Xe}$  in the lung decays corresponding to the longitudinal relaxation time  $T_1$  and the uptake (e.g., absorption, diffusion, or dissolution) of polarized  $^{129}\text{Xe}$  into the blood. From generally known oxygen related effects, the gas phase  $T_1$  for polarized  $^{129}\text{Xe}$  in the lungs is estimated at about 35 seconds. The decay time constant of magnetization in the lung due to blood uptake is generally described by the equation  $T_Q = V_L / (\lambda Q)$ . This equates to about 500 seconds and therefore presents a negligible polarization or magnetization decay of the lung gas over the breath-hold period. The effective  $T_1$  is reduced to about 33 seconds when this effect is included. For  $T_B = 10$  seconds, the  $^{129}\text{Xe}$  magnetization in the lung (and the associated dissolved or perfused  $^{129}\text{Xe}$  magnetization or polarization) will be reduced according to the equation ( $e^{-10/33} = .74$ ) of the starting magnetization value.

In a preferred embodiment, the pulse repetition time  $T_R$  is selected for optimal image contrast where  $T_R$  is less than or equal to  $t_p$  (the time it takes for the blood with the dissolved polarized  $^{129}\text{Xe}$  to travel from the lungs to the heart). As noted above, a

shortened  $T_R$  emphasizes signal from capillary beds while a longer  $T_R$  can show substantially all of the pulmonary vasculature.

As noted above, the dissolved phase imaging can be used to advantageously detect a pulmonary embolus. As will be appreciated by one of skill in the art, emboli  
5 tend to occur in the arterial side of the pulmonary vasculature, while the  $^{129}\text{Xe}$  uptake tends to occur on the venous side of the pulmonary vasculature. However, it is believed that symmetry in the venous-arterial branching will allow arterial defects to appear on the venous side. For example, for a patient with a blood clot or obstruction in the left pulmonary artery which occludes substantially all blood flow, then the  
10  $^{129}\text{Xe}$  dissolved phase image will show minimal or no left lung vasculature in the image because there is no flow to carry the polarized xenon from the capillary beds forward. Similarly, if the obstruction or clot is in the first branch of the left pulmonary artery, the corresponding dissolved phase ("perfusion") image will not show a portion of the venous vasculature before the first branching on the venous  
15 side. Further, when imaging to detect emboli, sufficient resolution techniques should be employed to help assure that any embolus in a given arterial vessel is detected. Thus, image resolution should be such that it corresponds to typical embolism size, vasculature location and vasculature structure (venous branching).

In a preferred embodiment, due to the approximately 200 p.p.m. chemical shift  
20 between the gas and dissolved phase resonance of the polarized  $^{129}\text{Xe}$ , at least two images including both a perfusion and ventilation image is generated on a patient during the same imaging session ("differential" imaging). Advantageously, differential images provide additional image information. For example, the differential image can help distinguish between a pulmonary embolus and a matched  
25 ventilation/perfusion defect associated with a structural anomaly. In one embodiment, the inhalation image is generated using polarized  $^3\text{He}$  while the perfusion image uses polarized  $^{129}\text{Xe}$ . Preferably, the images are generated from two data sets captured on two separate imaging sequences. For images using  $^{129}\text{Xe}$  as both the inhalation and perfusion medium, the same breath-hold delivery cycle can be employed for both sets  
30 of image data. In such an embodiment, it is preferred that the perfusion image is generated during the first 10 seconds of the breath-hold cycle and the remaining gas in the lung is used for a ventilation image, *i.e.*, the last five seconds of the delivery cycle. Of course, separate breath-hold delivery cycles can also be used. In any event.



differential imaging will allow better images with information which correlates the total region (lung space and boundary regions). This should also produce images which detect emboli, perfusion defects, and other circulatory system problems in the pulmonary and/or cardiac vasculature.

5

#### Cardiac Imaging Method

Similar to the pulmonary vasculature imaging method described above, the instant invention also includes cardiac imaging methods using dissolved hyperpolarized  $^{129}\text{Xe}$  to image the heart and cardiac blood vessels (in particular, major cardiac blood vessels). As described above, after inhalation, the dissolved phase  $^{129}\text{Xe}$  is transported in the blood flow path of the pulmonary vasculature to the heart. Subsequent to inhalation, at least a portion of the polarized gas enters into a dissolved state which enters the pulmonary vasculature, including the boundary tissue, cells, membranes, and pulmonary blood vessels such as capillaries, venules, veins, and the like. More specifically, a substantial amount of the dissolved polarized  $^{129}\text{Xe}$  ultimately enters the blood stream with an associated perfusion rate and cycles to the heart via the left atrium, then to the left ventricle and out of the heart. Generally stated, as will be appreciated by those of skill in the art, there is limited or no vascular branching in the blood flow path of the heart until after the left ventricle. As such, imaging the left side of the heart (atrium and ventricle) can be performed with the dissolved phase polarized  $^{129}\text{Xe}$  in the associated blood flow path similar to the methods described for imaging the pulmonary vasculature discussed above. Like the pulmonary imaging method, it is preferred that large angle excitation pulses are generated in a MRI system and that those pulses are timed in accordance with the blood replenishment rate to the region of interest.

The inhaled polarized  $^{129}\text{Xe}$  in the lung gas space acts as a substantially continuous supply of polarized  $^{129}\text{Xe}$  for dissolution and entry into the pulmonary blood. Preferably, the large angle pulse "selectively" excites only the blood-dissolved  $^{129}\text{Xe}$ , leaving the lung with a sufficient quantity of polarized gas at a sufficient polarization level (i.e., magnetized) and thus available for a substantially continuous supply for the gas to migrate to and enter a dissolved phase in the pulmonary vasculature, and ultimately the associated blood stream during the imaging procedure. As before, the timing of the RF pulses are dependent on the volume of the region to

be imaged ("V") and the blood flow rate (Q) as expressed by equation (4). The volume of the left ventricle (V) varies between about 140 ml and 60 ml depending on the phase of the cardiac cycle. The blood flow rate (Q) is estimated as above (at about 80 cc/s), while  $t_p$  for the left ventricle is estimated to be above 0.5 and below 2  
 5 seconds. More particularly, using the above stated parameters,  $t_p$  is estimated as between about 0.8-1.8 seconds;  $0.8s \leq t_p \leq 1.8s$ . Accordingly, it is preferred that the RF pulse repetition interval  $T_R$  be set such that it is less than or equal to the corresponding blood flow time  $t_p$ . Of course, any initial pulse should be timed to allow the dissolved  $^{129}\text{Xe}$  to be transported to the heart (*i.e.*, 2.5-3.5 seconds after  
 10 inhalation). Subsequent pulses are preferably timed to obtain signals from the dissolved polarized gas while minimizing the destruction of incoming magnetization. This will allow additional excitation pulses without waiting for the entire vasculature to be refilled with unaffected dissolved polarized gas.

The cardiac imaging method also can be beneficially used to image the heart  
 15 beyond the left ventricle 5. **Figure 4** shows a section view of the heart 15 with the lungs 25. As shown, the heart 15 includes left and right ventricles 5, 20 and the aorta 8. As also shown, the lungs 25 include right and left lungs 10, 15. As illustrated by **Figures 4 and 5**, blood flows from the left ventricle 5 up the ascending aorta 8a where the first branching is to the coronary arteries 9r, 9l. Perfusion imaging (dissolved  
 20 phase polarized  $^{129}\text{Xe}$  imaging) of these coronary arteries 9r, 9l can provide valuable information about the condition and status of these arteries, such as blockage, thickening, and the like. As shown in **Figure 5**, continuing along the blood flow path after the coronary arteries 9r, 9l, is the aortic arch 8b, a quadruple branching at the top of the arch 8c (to the right and left carotid arteries and the right and left subclavian  
 25 arteries) and then the descending aorta 8d. As the dissolved  $^{129}\text{Xe}$  flows along this blood flow path, the signal is sufficiently strong as to render clinically useful images. In summary, the imaging methods of the present invention can render clinically useful images of target regions which include, but are not limited to, the left and right pulmonary veins and associated capillaries, the left atrium and left ventricle, the  
 30 myocardium, the ascending aorta, the coronary arteries, the aortic arch, the descending aorta, the left and right subclavian arteries, and the left and right carotid arteries. Of course, using polarized gas with increased polarization levels (*i.e.*, above 20%) can further expand the dissolved phase imaging regions.

Further, it is anticipated that perfusion images according to the methods of the instant invention can be used in regions or organs which absorb or pass blood such as, the brain, the liver, and the kidney. In this application, one can use the methods as described herein, recognizing that some of the polarized dissolved-phase  $^{129}\text{Xe}$  will be retained in the respective tissues at different chemical shifts. However, as described above, volume calculations of the region or area of interest can be used to determine the pulse repetition rate to maximize the use of the dissolved polarization-related signal.

In a preferred embodiment, the method of the present invention uses a small close-fitting cardiac surface coil to deliver the excitation pulse rather than a conventional body coil. This will allow improved SNR and spatially limit the RF pulse to this smaller region, thereby minimizing the incidental destruction of the  $^{129}\text{Xe}$  incoming from the pulmonary vasculature.

In an additional preferred embodiment, the method of the present invention uses a pulse and gradient combination which is selective. This selection can be slice or volume selective. Conventional imaging methods are generally "slice" selective. Slice selective images are typically generated by combining a frequency-selective pulse in the presence of a z field gradient (" $G_z$ "), excitation can be confined to a slice of thickness " $\Delta z$ " along the z axis. The z field is defined as the axis which extends along the length of the body. The frequency bandwidth of the excitation pulse together with the gradient, confines excitation to the nuclei in the slice, substantially no signals are excited or detected from areas outside the defined slice.

Volume-selective imaging allow a two-dimensional spatial localization using a single pulse. These methods employ RF pulse/gradient combinations which excite a filled cylinder of spins. In a preferred embodiment, a volume-selective pulse is used, and more preferably, a cylindrical imaging volume selection is used. It is believed that the volume selection is particularly suitable for cardiac perfusion images because they can advantageously allow coronary artery images while also minimizing background signal from the left side of the heart. See C.J. Hardy and H. E. Cline, *Broadband nuclear magnetic resonance pulses with two-dimensional spatial selectivity*, J. Appl. Phys., 66(4), 15 August 1989; C. J. Hardy et al., *Correcting for Nonuniform k-Space Sampling in Two Dimensional NMR Selective Excitation*, 87 Jnl.

Magnetic Resonance, 639-645 (1990); and *Spatial Localization in Two Dimensions Using NMR Designer Pulses*, Jnl. of Magnetic Resonance, 647-654(1989).

A pulse-gradient combination can also limit the collateral damage to the incoming magnetization, thereby maximizing the image SNR. It is also preferred that multiple echo signals be used (*i.e.*, multiple gradient-recalled or RF-recalled echoes) to increase image SNR (linearly) with the number of echoes as discussed under the pulmonary imaging method.

An additional alternative to cardiac imaging is to directly deliver polarized  $^{129}\text{Xe}$  to a region of the heart (such as via injection and the like into the left ventricle muscle) to image the perfusion of the heart. Delivery directly to the right atrium/ventricle can allow perfusion imaging of the return side of the heart. In any event, the polarized  $^{129}\text{Xe}$  delivery can be via injection of various phases/vehicles such as but not limited to gaseous, dissolved, or liquid phase. Conventional image perfusion methods for this area employ radioactive tracers such as Thallium ( $^{201}\text{Tl}$ ) or Technetium ( $^{99\text{m}}\text{Tc}$ ). Using xenon, which is an inert noble gas, can beneficially replace radioactive tracers which can expose the subject to potentially dangerous elements.

#### Methods to Evaluate Blood Flow.

In addition to the imaging methods described above, the instant invention also includes MR spectroscopic methods which can be used to evaluate the lung and heart blood flow by using the dissolved-gas phase of the  $^{129}\text{Xe}$  inhaled gas which enters the vasculature (lung perfusion) and the blood stream as described above. Generally described, the instant method is relatively inexpensive and advantageously employs the inhaled hyperpolarized  $^{129}\text{Xe}$  (as discussed above) to evaluate blood flow in a low-field NMR spectroscopy system. The terms "evaluate" and "evaluating" as used herein are intended to be interpreted broadly and mean that the blood flow of a subject is measured, determined, quantified, observed, monitored, imaged, and/or assessed.

The term "blood flow" as used herein is to be broadly construed. Methods of evaluating blood flow according to the present invention encompass methods of determining blood flow rates, perfusion (typically measured in ml/min/g tissue), comparative blood flow values (monitoring blood volume or flow rates as changes over time such as before and after drug therapy or surgical treatment or real time feed

back during surgery to verify success of treatment--without the need for absolute values), blood volume, or blood path anomalies, in particular, in the pulmonary and/or cardiac vasculature. Also included in the inventive methods of evaluating blood flow are methods of determining the presence of absence of an obstruction to blood flow or  
 5 local defects in blood passage through the vasculature (*e.g.*, from stenosis), in particular, the pulmonary and/or cardiac vasculature.

As described above (such as in Equations 1-6), a patient who inhales 1 L of Xe into the lungs (having about a 6 L lung volume) will yield about or dissolve into about 1/6 of that value of the xenon concentration (.02 amagat) in the pulmonary  
 10 vasculature and associated blood. In a preferred embodiment, the method uses frequency selective large angle (more preferably 90°) RF excitation pulses which substantially depletes the  $^{129}\text{Xe}$  in the pulmonary blood but leaves the hyperpolarized gas in the lungs substantially undisturbed. In this embodiment, the repetition time interval between RF pulses ( $T_R$ ) and the pulmonary blood flow rate ( $Q$ ) can be used to  
 15 determine the effective pulmonary volume ( $V_{\text{eff}}$ ) containing (dissolved phase) hyperpolarized  $^{129}\text{Xe}$ . See equation 6, *supra*. This relationship assumes that  $T_R$  is less than or substantially equal to the time it takes for the polarized  $^{129}\text{Xe}$  to leave the pulmonary blood ( $t_p$ ). As discussed above, for typical blood flow rate and estimated volume of venous pulmonary blood,  $t_p$  is approximately 2.5 seconds. Thus, with a  
 20 large RF excitation pulse (preferably, about  $\alpha=90^\circ$ ), the dissolved pulmonary  $^{129}\text{Xe}$  signal strength in the pulmonary blood is proportional to the product of coil gain ("G"), Xe polarization (" $P_{\text{Xe}}$ "), and polarized Xe density or concentration in the vasculature ( $[\text{Xe}]_p=\lambda[\text{Xe}]_L$ ), which can be stated by the following expression:

$$25 \quad Sp(T_R) = GP_{\text{Xe}}\lambda[\text{Xe}]_L QT_R \quad (12)$$

Notably, the signal strength is dependent on both the pulse interval ( $T_R$ ) and the blood flow rate ( $Q$ ). The dissolved signal intensity versus repetition time will have an associated slope which can be mathematically expressed as follows:

$$30 \quad \frac{dS_p}{dT_R} = GP_{\text{Xe}}\lambda[\text{Xe}]_L Q \quad (13)$$

The slope is directly proportional to the pulmonary blood flow rate (Q). Calibration of the blood flow rate is obtainable by evaluating the gas phase signal ("S<sub>L</sub>") in the lung, the signal having an associated small RF tipping angle (excitation angle) ("α<sub>L</sub>"). The gas phase signal can be expressed by the equation:

5

$$S_L = GP_{Xe} [Xe]_L V_L \sin \alpha_L \quad (14)$$

The pulmonary blood flow rate (Q) can be stated by the ratio of the hyperpolarized <sup>129</sup>Xe gas and dissolved phase signals. This ratio cancels receiver gain (G) and polarization value P<sub>Xe</sub>. Accordingly, the blood flow rate (Q) can be expressed by the following:

10

$$Q = \frac{V_L \sin \alpha_L (dS_p / dT_R)}{\lambda S_L} \quad (15)$$

Advantageously, with measurements of the Xe/blood partition coefficient (λ) and the total lung volume (V<sub>L</sub>), a quantitative measurement of blood flow is established according to a method of the instant invention. As will be appreciated by one of skill in the art, lung volume can be easily established to about 20% accuracy with techniques known to those of skill in the art. Preferably, techniques with relatively improved accuracy such as but not limited to spirometry are used. Accordingly, the instant invention provides a clinically useful real-time blood measurement tool.

Further, and advantageously, MR spectroscopy using <sup>129</sup>Xe can be simpler and less expensive relative to the cost of other MR images. For example, the quantity of polarized gas needed, the polarization level of the polarized gas, and the isotopic enrichment can be reduced as compared to those used for conventional polarized gas MR imaging. In one embodiment, the spectroscopic perfusion measurement can be made with about 100 cc of unenriched gas polarized to only 1-2%. This is in comparison to a polarization of 20% for 500 cc of 80% isotopically enriched <sup>129</sup>Xe to yield a comparable MR image. Still another advantage is that the spectroscopic methods do not require a polarization calibration because the measurement is "self-

25

calibrating". Stated differently, the polarization is cancelled by comparing dissolved and gaseous xenon signal, both of which can be assumed to have identical polarization to the extent that T1 relaxation in the blood is negligible, which it is for short T<sub>R</sub> settings as discussed above. Other advantages include the use of low  
5 magnetic field systems, such as 0.1-1.0 Tesla, and preferably about .075-0.2 T, and more preferably about 0.1-.15T. The lower field limit is established by the length of the pulse needed to get selective excitation. For example, a 200 ppm shift at 1.5T means a frequency difference of about 3.52kHz. Thus, for a hard pulse, it is desired to have a pulse length of about 284μs so that the gas phase remains substantially or  
10 totally unexcited. Reducing the field by a factor of ten to .15T gives a frequency difference of .352KHz and the corresponding discriminating pulse length of about 2.84ms. Similarly, at .015T (150G), the pulse length is relatively long (28ms). The longer pulse time at this field strength T2 can potentially degrade the signal because T2 can dephase the signal before the pulse application is complete.

15 Advantageously, the method can be used successfully in systems having relatively poor magnet homogeneity because the field gradients do not adversely impact the spectroscopy perfusion method. By eliminating the necessity for these items, system operating costs can potentially be greatly reduced.

Further, a simplified and lower cost polarizer system can be used to polarize  
20 the <sup>129</sup>Xe for this method. For example, the low cost polarizer system can use a lower power optical laser (such as a 10 Watt laser) and reduced accuracy measurement and associated equipment attributed to the elimination of the need for accurate polarization, each of which can provide additional cost savings over that of other systems used for other imaging methods.

25 Preferably, the appropriate magnet homogeneity associated with a patient's chest area for the spectroscopy imaging method of the instant invention is estimated by the corresponding chemical shift of <sup>129</sup>Xe in the dissolved phase in the blood over that in the gaseous phase. This shift, as discussed above, is about 200 ppm. Thus, in order to achieve "selective" excitation of the dissolved phase, a field homogeneity of  
30 about 50 ppm or better is preferred. More preferably, a field homogeneity of about 20 ppm or better is used. In contrast, conventional MRI systems are shimmed to about 1ppm to operate with about a 1 ppm homogeneity. The lower limit of the magnetic field strength used in the spectroscopy method of the instant invention can be

determined by the pulse time used to selectively excite the dissolved phase (instead of the gas phase). The frequency difference ("Δν") between the gas and dissolved phase can be stated by:

$$\Delta\nu = \frac{\gamma}{2\pi} \delta B_0 \quad (16)$$

5

Wherein  $B_0$  is the strength of the magnetic field,  $\gamma$  is the gyromagnetic ratio of  $^{129}\text{Xe}$  and  $\delta$  is the chemical shift separating the gas and dissolved phases.

Accordingly, when applying a pulse which selectively excites one phase rather than the other, the length of the pulse should be sufficiently long to have a sufficiently narrow frequency bandwidth. For example, by Fourier analysis, a square excitation pulse of duration  $t_{rf}$  will have an frequency spectrum centered on the pulse frequency with a frequency width ("Δν<sub>rf</sub>") of about  $1/t_{rf}$ . Thus, for phase discrimination, the pulse frequency distribution width is preferably smaller than the frequency separation between the phases ( $\Delta\nu_{rf} < \Delta\nu$ ). Thus, the approximate lower field limit can be written as:

15

$$B_0 \geq \frac{2\pi}{\gamma \delta t_{rf}} \quad (17)$$

Although the pulse time  $t_{rf}$  can be as long as necessary to achieve dissolved phase discrimination at the given field strength, the pulse length time is also limited by the timescale of the blood flow effects ( $t_p$ ) as well as  $T_2$  and  $T_2^*$ . Preferably, a large number of pulses are generated during the time interval ( $t_p$ ). Preferably, at least 25 excitation pulses are applied during this interval, more preferably at least 50, and most preferably about 100 pulses. Assuming the time scale is about 2.5 seconds, as discussed above, then a preferable pulse time ( $t_{rf}$ ) is about 25 ms. For  $\gamma=7402\text{G}^{-1}\text{s}^{-1}$ , an exemplary minimum field strength is about 170 gauss ("G"). This is a relatively low field, approximately 1/100 the standard 1.5T imaging magnet.

25

In an additional embodiment of the spectroscopic blood flow method of the instant invention, pulmonary emboli or other blockage can be detected by measuring the pulmonary blood flow rate (Q). This measurement is based on normal blood flow



rates in healthy subjects. Preferably, the blockage detection method also considers heart rate. In a preferred embodiment, the detection method correlates the blood flow rate (Q) with heart rate ("R"). For example, the detection method preferably uses a normalized flow rate Q/R. Thus, as illustrated by **Figure 6**, the detection method

5 includes positioning a subject in a MR spectroscopy unit (**Block 500**) and delivering gaseous polarized  $^{129}\text{Xe}$  to the subject (**Block 510**). A portion of the gaseous  $^{129}\text{Xe}$  is dissolved into the pulmonary vasculature which has an associated perfusion or pulmonary blood flow path (**Block 520**). The blood flow is evaluated based on the spectroscopy signal of the dissolved  $^{129}\text{Xe}$  (**Block 530**). This method can yield unique

10 real-time information about blood flow and perfusion that is difficult to achieve by other means. In a preferred embodiment, the dissolved phase  $^{129}\text{Xe}$  is (selectively) excited with a large flip angle excitation pulse as described above (**Block 525**). It is also preferred that the pulse sequence be correlated with the blood volume (or flow rate) to maximize the signal with the magnetization in the blood.

15 Preferably, the method includes detecting blockage in the blood flow path of the subject based on the results of the measuring step. In one embodiment, the blood flow rates of healthy subjects are compared to the measured flow rate to perform the detecting step. In determining if there is a problem, the heart rate is taken into account. Accordingly, in a preferred embodiment, the method uses the heart rate of

20 the subject to normalize the measured blood flow rate.

Advantageously, for repetition times ( $T_R$ ) which are less than  $t_p$ , the signal will be substantially linear with  $T_R$ . In addition, an integrated signal versus  $T_R$  will be proportional to blood flow rate (Q). Thus, a substantially calibrated measurement of the blood flow rate (Q) can advantageously be obtained. This can be done relatively

25 inexpensively with a low field magnet and with low homogeneity requirements. Advantageously, such a calibration can be performed accurately and relatively simply.

In another preferred embodiment, a spectroscopic signal associated with the dissolved-phase  $^{129}\text{Xe}$  can be derived such that it represents a blood volume or blood flow rate. The patient can then be subjected to a drug therapy or surgery to treat a

30 cardiac or pulmonary vasculature or blood flow problem. A second signal can then be obtained and a comparative, relative, or percent increase (or decrease) in blood flow can be obtained without requiring an "absolute value" of blood volume. Such a comparative MR spectroscopy evaluation can be done in real-time to indicate during

surgery (such as during angioplasty) whether a blood flow path obstruction has been removed or diminished. Further, such a comparative measurement or evaluation can be used to determine whether drug therapy improved a patient's blood flow (by allowing an increased blood volume or rate (such as due to a less viscous blood or lipid management) and the like.

Additionally, due to the depolarizing effect of oxygen depleted blood on dissolved phase polarized  $^{129}\text{Xe}$ , MR spectroscopy signal intensity (reduced or increased) can be used to evaluate conditions associated with reduced or increased levels of oxygen along the xenon-blood barrier or blood flow path. The deoxyhemoglobin is paramagnetic and has a greater depolarizing effect on the dissolved phase  $^{129}\text{Xe}$ . The well oxygenated blood or tissue provide longer T1's compared to oxygen starved blood or tissue. Thus, a stronger spectroscopy signal relates to well oxygenated levels of oxygen in the tissue or blood while a weaker or lower spectroscopic polarization-based signal relates to oxygen-starved, depleted or deprived regions.

#### Other Embodiments.

The present invention has been described above with respect to particular preferred embodiments. Those skilled in the art, however, will appreciate that the invention can be employed for a broad range of applications. Methods for imaging or obtaining information about blood flow using dissolved hyperpolarized  $^{129}\text{Xe}$  can be carried out according to the present invention using magnetic resonance or spectroscopic techniques known to those skilled in the art. *See, e.g.*, U.S. Patent No. 5,833,947; U.S. Patent No. 5,522,390; U.S. Patent No. 5,509,412; U.S. Patent No. 5,494,655; U.S. Patent No. 5,352,979; and U.S. Patent No. 5,190,744. *See also* Hou et al., *Optimization of Fast Acquisition Methods for Whole-Brain Relative Cerebral Blood Volume (rCBV) Mapping with Susceptibility Contrast Agents*, 9 J. Magnetic Resonance Imaging 233 (1999); Simonsen et al., *CBF and CBV Measurements by USPIO Bolus Tracking: Reproducibility and Comparison with Gd-Based Values*, 9 J. Magnetic Resonance Imaging 342 (1999); Mugler III et al., *MR Imaging and Spectroscopy Using Hyperpolarized  $^{129}\text{Xe}$  gas: Preliminary Human Results*, 37 Magnetic Resonance in Medicine, pp. 809-815 (1997); Belliveau et al., *Functional Cerebral Imaging by Susceptibility-Contrast NMR*, 14 Magnetic Resonance in

Medicine 14 538 (1990); Detre et al., *Measurement of Regional Cerebral Blood Flow in Cat Brain Using Intracarotid  $^2\text{H}_2\text{O}$  and  $^2\text{H}$  NMR Imaging*, 14 Magnetic Resonance in Medicine 389 (1990); Frank et al., *Dynamic Dysprosium-DTPA-BMA Enhanced MRI of the Occipital Cortex: Functional Imaging in Visually Impaired Monkeys by PET and MRI* (Abstract), Ninth Annual Scientific Meeting and Exhibition of the Society of Magnetic Resonance In Medicine (August 18-24, 1990); Le Bihan, *Magnetic Resonance Imaging of Perfusion*, 14 Magnetic Resonance in Medicine 283 (1990); and Rosen et al., *Perfusion Imaging by Nuclear Magnetic Resonance*, 5 Magnetic Resonance Quarterly 263 (1989). The contents of these documents are hereby incorporated by reference as if recited in full herein.

In particular embodiments, the present invention can be practiced to give a quantitative assessment of blood flow (more preferably, perfusion) as will be appreciated by one of skill in the art. According to this embodiment, signal intensity can be followed over time, and the area under the resulting curve can be integrated to give a quantitative measure of blood flow. Examples of such quantitative relationships were developed for use with radioactive contrast agents with MR imaging and spectroscopy methods may be particularly suitable for dissolved phase  $^{129}\text{Xe}$  analysis of blood vessels. See, generally, Lassen, *Cerebral Transit of an Intravascular Tracer may Allow Measurement of regional Blood Volume but not Regional Blood Flow*, 4 J. Cereb. Blood Flow and Metab. 633 (1984). However, it will be appreciated by one of skill in the art, that, unlike the radioactive contrast agents, the polarized states of both the gas and the dissolved phase gas (in the body of a subject) are relatively short and "automatically" terminate within the body within blood within less than about 1-2 minutes (depending on the polarization level) from the time when the inhalation procedure or gaseous supply is terminated at the lungs. Therefore, after about 1 minute, there is typically no "residue" polarized gas to image or to generate an MR detectable signal to potentially interfere with MR signal evaluations.

Furthermore, the inventive methods may be used for wide range of diagnostic and evaluative applications, preferably those related to cardiac, pulmonary or cardiovascular function, as described in more detail below.

In preferred embodiments, the inventive methods are used to determine perfusion rates (e.g., absolute and/or relative perfusion), and more preferably to identify and/or assess the severity of abnormal perfusion. In other particular

embodiments, temporal variations in blood flow are determined, *e.g.*, to assess the effects of a vasoconstrictory or vasodilatory substance and/or to identify regions of surgically induced variations in blood perfusion.

Other applications of the present invention include, but are not limited to:

- 5 identification and assessment of the presence or absence and/or severity of cardiac ischemias and/or infarcts; localization and assessment of thrombi and plaques; determination of "therapeutic windows" for administering heparin, vasodilators, antihypertensive agents, calcium antagonists and the like, *e.g.*, in reversible focal ischemia; monitoring of other induced vasodilator effects; detection and quantitative  
10 evaluation of the severity of ischemias; monitoring the vasodilatory or vasoconstrictory effects of a physiologically active substance; and monitoring surgically induced blood perfusion variations.

- The present invention may further be employed for: assessment of cerebral perfusion in following induced subarachnoid hemorrhage or in conditions marked by  
15 brain dysfunction, *e.g.*, in connection with acute severe symptomatic hyponatremia; evaluation of new therapies, *e.g.*, in the treatment of cerebral vasospasm (including but not limited to, anti-thrombolytic therapies, calcium channel blockers, anti-inflammatory therapies, angioplasty, and the like); assessment of the presence or absence and/or severity of ischemia in large tissue masses; assessment of the  
20 relationship between blood metabolites and cerebral perfusion in cerebral ischemia associated with acute liver failure, *e.g.*, for the treatment of Alzheimer's disease; evaluation of new therapies for stroke, including but not limited to, t-PA, aspirin antiphospholipids, lupus anticoagulants, antiphospholipid antibodies, and the like; evaluation of risk factors for stroke, *e.g.*, serum lipid levels; evaluation of induced  
25 brain hypothermia on cerebral perfusion during neurosurgery, *e.g.*, for stroke; evaluation of the effects of age on cerebral perfusion, *e.g.*, to study lacunar infarcts; and assessment of narcotics, *e.g.*, cocaine, amphetamines, ethanol, and the like, on the ischemic brain.

The present invention finds use for both veterinary and medical applications:

- 30 The present invention may be advantageously employed for diagnostic evaluation and/or treatment of subjects, in particular human subjects, because it may be safer (*e.g.*, less toxic) than other methods known in the art (*e.g.*, radioactive methods). In general, the inventive methods will be more readily accepted because they avoid

radioactivity or toxic levels of chemicals or other agents. Subjects according to the present invention can be any animal subject, and are preferably mammalian subjects (*e.g.*, humans, canines, felines, bovines, caprines, ovines, equines, rodents, porcines, and/or lagomorphs), and more preferably are human subjects.

5           The foregoing is illustrative of the present invention and is not to be construed as limiting thereof. Although a few exemplary embodiments of this invention have been described, those skilled in the art will readily appreciate that many modifications are possible in the exemplary embodiments without materially departing from the novel teachings and advantages of this invention. Accordingly, all such modifications  
10   are intended to be included within the scope of this invention as defined in the claims. In the claims, means-plus-function clause are intended to cover the structures described herein as performing the recited function and not only structural equivalents but also equivalent structures. Therefore, it is to be understood that the foregoing is illustrative of the present invention and is not to be construed as limited to the specific  
15   embodiments disclosed, and that modifications to the disclosed embodiments, as well as other embodiments, are intended to be included within the scope of the appended claims. The invention is defined by the following claims, with equivalents of the claims to be included therein.

## THAT WHICH IS CLAIMED IS:

1. A method for MRI imaging the pulmonary and/or cardiac vasculature using dissolved-phase polarized  $^{129}\text{Xe}$ , comprising the steps of:
  - positioning a patient in an MRI apparatus having a magnetic field associated therewith;
  - 5 delivering polarized  $^{129}\text{Xe}$  gas to a predetermined region of the patient's body, the polarized gas having a dissolved imaging phase associated therewith;
  - exciting a predetermined region of the patient's body having a portion of the dissolved phase polarized gas therein with at least one large flip angle RF excitation pulse; and
  - 10 acquiring at least one MR image associated with the dissolved phase polarized gas after said exciting step.
2. A method according to Claim 1, wherein said exciting step is repeated within a predetermined repetition time, the predetermined repetition time being less than the time it takes for a given volume of blood to move from the lungs to the heart.
3. A method according to Claim 1, wherein the large flip angle excitation pulse is about a 90 degree excitation pulse.
4. A method according to Claim 1, wherein the RF excitation pulse has a pulse frequency, and wherein the pulse frequency is selected such that it corresponds to the dissolved phase polarized gas resonance.
5. A method according to Claim 3, wherein the repetition time is less than about 3 seconds.
6. A method according to Claim 1, wherein the large angle pulse selectively excites substantially only the dissolved phase of the  $^{129}\text{Xe}$ .
7. A method according to Claim 1, wherein the excitation pulse has a duration which is less than about 2.5 milliseconds.

8. A method according to Claim 1, wherein the predetermined region is the patient's blood volume in the vasculature between and/or within the lungs and the heart.

9. A method according to Claim 1, wherein said delivering step includes having the patient inhale the polarized  $^{129}\text{Xe}$  gas into the lungs, the  $^{129}\text{Xe}$  having a gas phase resonance which is higher than the dissolved-phase resonance, and wherein at least a portion of the  $^{129}\text{Xe}$  gas enters into the pulmonary vasculature in a dissolved-phase, and wherein at least a portion of the dissolved-phase  $^{129}\text{Xe}$  then enters the blood stream with an associated perfusion rate.

10. A method according to Claim 9, wherein a differential MRI image is obtained which includes information corresponding to both the  $^{129}\text{Xe}$  gas and dissolved-gas phase, and wherein said differential image is obtained by exciting the  $^{129}\text{Xe}$  gas phase with an RF pulse having an excitation pulse frequency which corresponds to the resonance of the gas phase and exciting the dissolved phase with an RF pulse having an excitation frequency which corresponds to the resonance of the dissolved phase, and wherein the gas phase RF excitation pulse is a small flip angle pulse and the dissolved phase RF excitation pulse is a large flip angle pulse.

11. A method according to Claim 9, wherein said method further comprises the step of delivering via inhalation a quantity of polarized  $^3\text{He}$  gas, and wherein a MRI differential image is obtained which includes information corresponding to the polarized gas  $^3\text{He}$  in the lungs in addition to the information corresponding to the dissolved phase polarized  $^{129}\text{Xe}$ .

12. A method according to Claim 9, wherein said inhalation delivering step includes a breath-hold delivery period.

13. A method according to Claim 12, wherein the breath-hold period is at least 10 seconds.

14. A method according to Claim 9, wherein the at least one image is a multi-echo image.

15. A method according to Claim 14, wherein the multi-echo image is one of a slice selective and volume selective image pattern.

16. A method according to Claim 2, wherein the repetition time is decreased to emphasize a signal associated with capillaries in the pulmonary region.

17. A method according to Claim 2, wherein the repetition time is increased to include distal vasculature relative to the pulmonary capillaries.

18. A method according to Claim 1, wherein dissolved-phase  $^{129}\text{Xe}$  has an associated decay time constant (T1) corresponding to its polarization life and a transverse relaxation time in blood ( $T_2^*$ ), and wherein for  $T_2^*$  greater than about 100ms, said acquiring step employs one of EPI and RARE multi-echo imaging methods.

19. A method according to Claim 1, wherein said acquiring step acquires at least 32 echoes per each excitation pulse.

20. A method according to Claim 9, wherein cardiac gating is used so that said acquiring step is timed such that it is performed during slow blood flow periods.

21. A method according to Claim 14, wherein the multi-echo imaging uses one of gradient recalled and RF recalled echoes.

22. A method for evaluating the blood flow of a patient, comprising the steps of:

positioning a subject in a MR spectroscopy system capable of detecting spectroscopic signals in a subject having a pulmonary vasculature;

5 delivering gaseous polarized  $^{129}\text{Xe}$  to the subject;



dissolving a portion of the gaseous polarized  $^{129}\text{Xe}$  into the pulmonary vasculature having an associated blood flow path;

exciting the dissolved portion of the  $^{129}\text{Xe}$  with an MR spectroscopy RF excitation pulse; and

10 evaluating blood flow of the patient based on a spectroscopic signal corresponding to the dissolved polarized  $^{129}\text{Xe}$ .

23. A method according to Claim 22, further comprising the step of identifying one or more of: (a) perfusion deficits in the pulmonary vasculature or the cardiac vasculature, (b) pulmonary vasculature emboli, (c) blood flow related circulatory system deficits, and (d) restrictions and obstructions in the blood flow path  
5 of the subject based on said evaluating step.

24. A method according to Claim 21, wherein said evaluating step includes a measuring step which quantifies the subject's blood flow rate.

25. A method according to Claim 24, wherein said measuring step uses the heart rate of the subject to normalize the measured blood flow rate.

26. A method according to Claim 22, wherein said evaluating step includes the steps of exciting the dissolved  $^{129}\text{Xe}$  with a large angle RF excitation pulse.

27. A method according to Claim 26, wherein said large angle pulse is above about a 90 degree flip angle pulse, and wherein said delivering step is performed by the subject inhaling a quantity of gaseous polarized  $^{129}\text{Xe}$ .

28. A method according to Claim 27, wherein said exciting step is performed selectively to excite the dissolved  $^{129}\text{Xe}$  and leave the gaseous  $^{129}\text{Xe}$  substantially undisturbed.

29. A method according to Claim 22, wherein said evaluating step includes the step of comparing the blood flow rates of healthy subjects with the measured blood flow rate.

30. A method according to Claim 26, wherein the MR Spectroscopy System includes a magnetic field operably associated therewith, and wherein the magnetic field is less than about .5T.

31. A method according to Claim 30, wherein said evaluating step is performed to provide real-time blood flow information.

32. A cardiac imaging method, comprising the steps of:  
positioning a subject having a cardiac blood flow path in an MRI system;  
delivering polarized  $^{129}\text{Xe}$  to the subject;  
dissolving at least a portion of the polarized  $^{129}\text{Xe}$  into the subject's cardiac  
5 blood flow path:  
exciting dissolved polarized  $^{129}\text{Xe}$  in a target region along the blood flow path  
with at least one large angle RF excitation pulse; and  
generating a MR image associated with the excited dissolved polarized  $^{129}\text{Xe}$ .

33. A method according to Claim 32, wherein said delivering step is performed by the subject inhaling a quantity of gaseous  $^{129}\text{Xe}$ .

34. A method according to Claim 33, wherein said positioning step includes positioning the patient in close proximity to a cardiac coil configured to spatially limit the excitation pulses transmitted to the subject.

35. A method according to Claim 34, wherein said generating step uses a volume selective pulse-gradient combination.

36. A method according to Claim 32, wherein said exciting step is directed to the target imaging region such that said exciting step is selectively delivered to spatially limit the depolarizing effect of the excitation pulse on the polarized gas outside the selected imaging region.

37. A method according to Claim 33, wherein said excitation pulse has a frequency which corresponds to the resonance of the dissolved polarized  $^{129}\text{Xe}$ , and

wherein the excitation frequency is selected such that it has a narrow frequency bandwidth.

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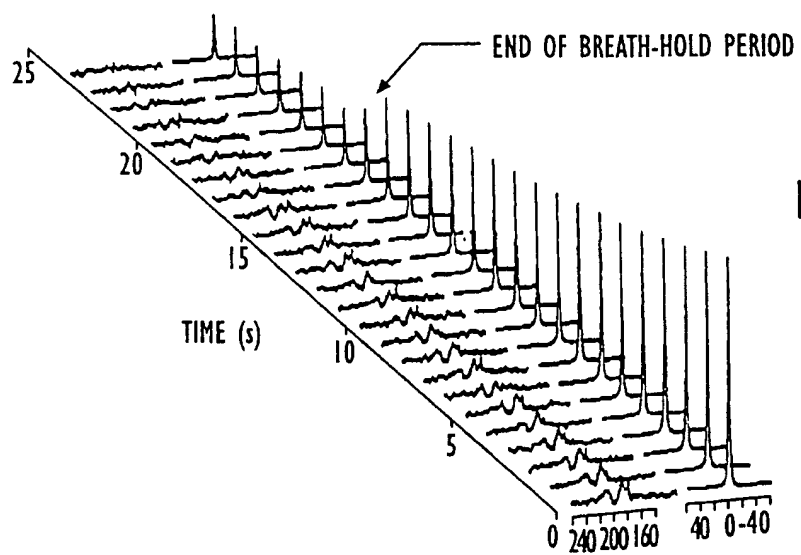


FIG. 1.

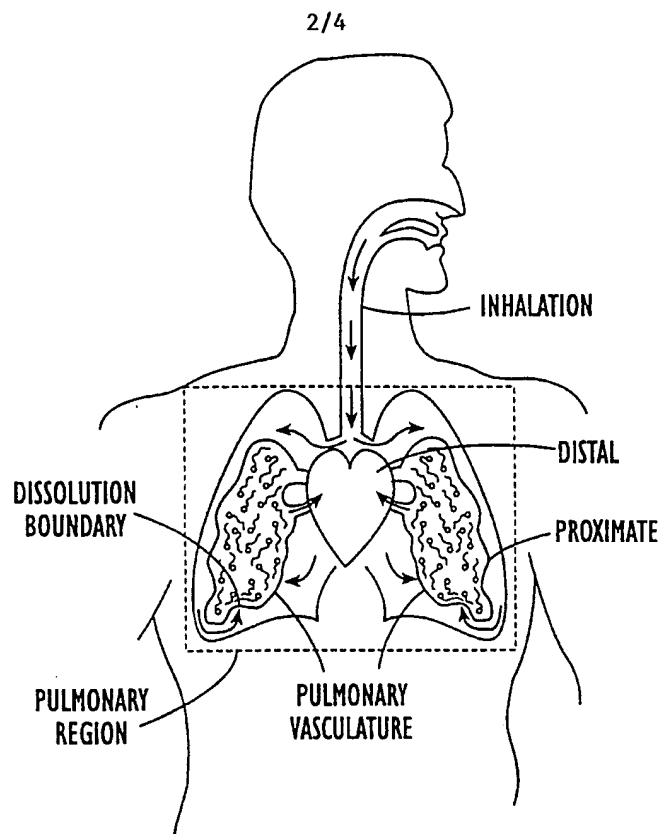


FIG. 2.

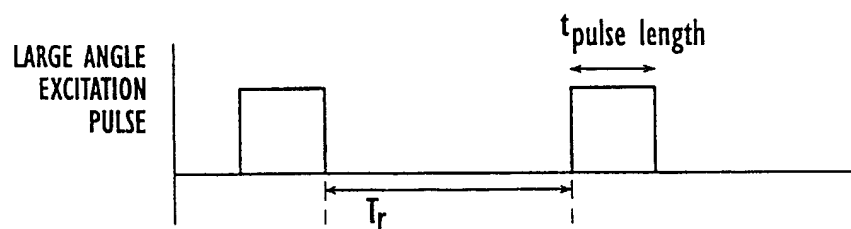


FIG. 3.

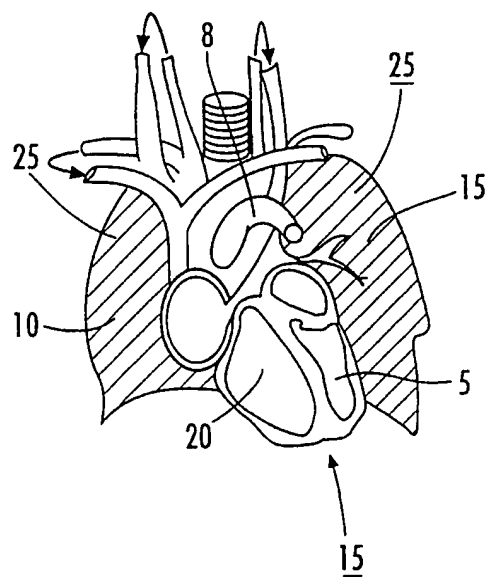


FIG. 4.

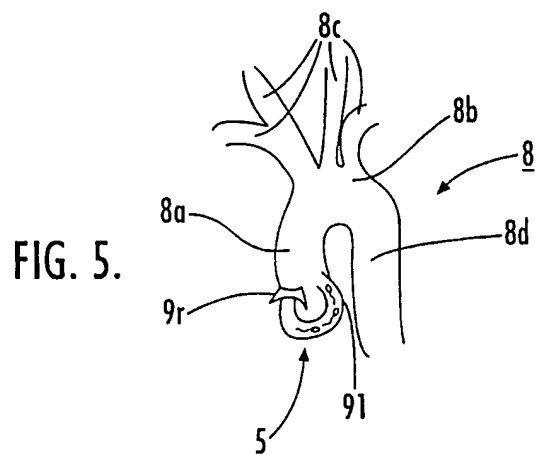


FIG. 5.

4/4

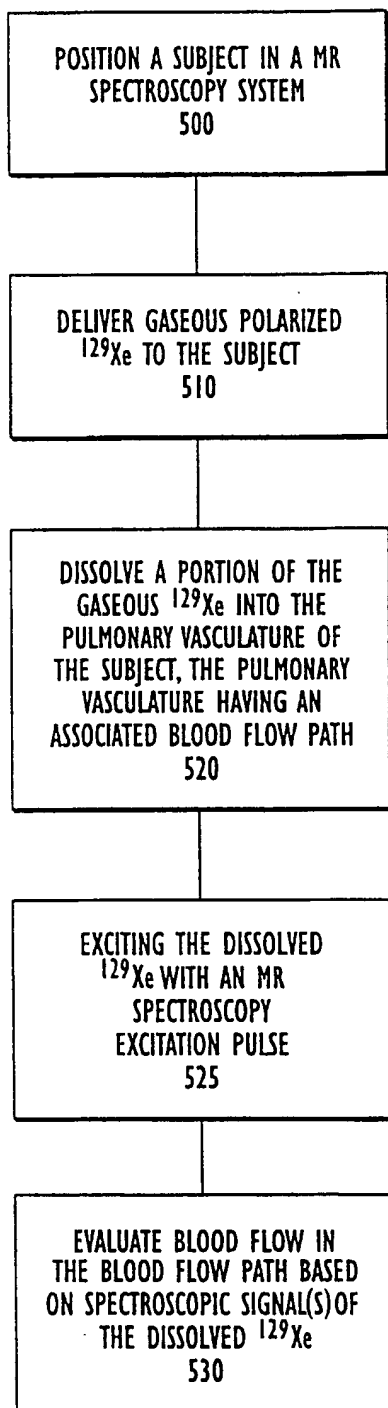


FIG. 6.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/05788

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 G01R33/28

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 G01R

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JIA-HONG GAO ET AL: "Magnetization and diffusion effects in NMR imaging of hyperpolarized substances" MAGNETIC RESONANCE IN MEDICINE, JAN. 1997, WILLIAMS & WILKINS, USA, vol. 37, no. 1, pages 153-158, XP000749406 ISSN: 0740-3194 see the whole document	1-10, 14, 15, 21-29, 32-37
Y	---	11-13, 16-19, 30, 31
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search

2 August 1999

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/05788

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 27438 A (UNIV NEW YORK ;UNIV PRINCETON (US)) 19 October 1995 (1995-10-19) cited in the application page 7, line 13 - page 9, line 22 page 20, line 23 - page 22, line 24 page 32, line 4 - page 34, line 10 ---	11
Y	MUGLER J P ET AL: "MR IMAGING AND SPECTROSCOPY USING HYPERPOLARIZED 129XE GAS: PRELIMINARY HUMAN RESULTS" MAGNETIC RESONANCE IN MEDICINE, vol. 37, no. 6, 1 June 1997 (1997-06-01), pages 809-815, XP000655650 ISSN: 0740-3194 cited in the application see the whole document ---	12,13
Y	CHEN X J ET AL: "MR microscopy of lung airways with hyperpolarized /sup 3/He" MAGNETIC RESONANCE IN MEDICINE, JAN. 1998, WILLIAMS & WILKINS, USA, vol. 39, no. 1, pages 79-84, XP002111039 ISSN: 0740-3194 see the whole document ---	16,17
Y	ZHAO LEI ET AL: "Biomedical imaging using hyperpolarized noble gas MRI: Pulse sequence considerations" 7TH RCNP INTERNATIONAL WORKSHOP ON POLARIZED /SUP 3/HE BEAMS AND GAS TARGETS AND THEIR APPLICATION, KOBE, JAPAN, 20-24 JAN. 1997, vol. 402, no. 2-3, pages 454-460, XP004107387 Nuclear Instruments & Methods in Physics Research, Section A (Accelerators, Spectrometers, Detectors and Associated Equipment), 11 Jan. 1998, Elsevier, Netherlands ISSN: 0168-9002 see the whole document ---	18,19
Y	BLACK R D ET AL: "In vivo He-3 MR images of guinea pig lungs" RADIOLOGY, JUNE 1996, RADIOD. SOC. NORTH AMERICA, USA, vol. 199, no. 3, pages 867-870, XP002111040 ISSN: 0033-8419 see the whole document ---	30,31
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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 99/05788

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	<p>WAGSHUL M E ET AL: "In vivo MR imaging and spectroscopy using hyperpolarized /sup 129/Xe"</p> <p>MAGNETIC RESONANCE IN MEDICINE, AUG. 1996, WILLIAMS &amp; WILKINS, USA, vol. 36, no. 2, pages 183-191, XP002070307</p> <p>ISSN: 0740-3194</p> <p>see the whole document</p> <p>-----</p>	1,22,32

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Information on patent family members

International Application No

PCT/US 99/05788

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